Pharmaceutical preparation

The invention relates to a novel stable pharmaceutical preparation comprising levothyroxine sodium, gelatine and fillers and which is free of organic solvent residues.

This novel preparation has an improved stability and can be used as a thyroid hormone preparation.

This novel preparation furthermore has an improved release of active compound in vitro.

The invention was based on the object of making available novel medicaments in the form of pharmaceutical preparations, which have better properties than known medicaments used for the same purposes.

In the Federal Register Vol. 62, No. 15, August 14, 1997; page 43535, the Department of Health and Human Services, Food and Drug Administration, published the facts that the products available on the US market which comprise levothyroxine sodium and are orally administered have stability problems and therefore must be present in an up to 20% excess dose and that manufacturers must develop appropriate novel administration forms. The requirements on in-vitro release for levothyroxine Na tablets have furthermore been increased. The monograph draft version of the Pharmacopeial Forum (Pharm. Preview, **1995**, *21*, 1459-1461) proposes, in addition to the valid Test 1 (phosphate buffer pH 7.4, in 80 minutes > 55%) to approve Test 2 (water in 45 minutes > 70%).

This object was achieved by the discovery of the novel preparation.

Thyroxine-containing preparations with other additives such as glycine, a carbohydrate and an inorganic salt are disclosed in WO 97 17 951.
Another thyroxine preparation stabilized with thiosulfate is described in DE 195 41 128.

A combination preparation comprising levothyroxine sodium and potassium iodide is known from US 5,635,209.
Another thyroxine-containing formulation which contains thyroxine/cyclodextrin complexes is described in WO 97 19 703.

In addition to levothyroxine sodium, the pharmaceutical formulation according to the invention can also contain liothyronine sodium.

The invention preferably relates to a pharmaceutical preparation as described, characterized in that it contains 5 to 400 µg, preferably 10 to 300 µg, in particular 25 to 300 µg, of levothyroxine sodium.

The invention furthermore preferably relates to a pharmaceutical preparation as described, characterized in that it contains levothyroxine sodium micronized with a particle size of between 5 µm and 25 µm.

The invention furthermore preferably relates to a pharmaceutical preparation as described, characterized in that it contains fillers selected from the group consisting of lactose and/or maize starch and/or microcrystalline cellulose.

A particularly preferred pharmaceutical preparation is one characterized in that it is a solid preparation in the form of tablets.

Particularly preferred embodiments contain 25, 50, 75, 100, 125, 150, 175 or 200 µg of levothyroxine sodium.

The active compound(s) is/are sensitive to light, heat and oxygen. On account of this known instability, the active compound is in an excess dose of up to 5% in the formulations.

The preparation according to the invention has a surprising stability when gelatine is used as a binder.

If this is replaced by another customary binder such as Methocel, even at the start of the stability investigations a decline in the active compound content is detected and furthermore the sum of the by-products is increased.

If, for example, the starting value of active compound is determined in a 100 µg batch in which gelatine has been replaced by Methocel, instead of the 105% to be expected only 100.48% is found.

Stability investigations show that the tablets according to the invention which contain levothyroxine sodium are stable for at least 2 years if they are stored at temperatures below 30°C.

Furthermore, the release of the active compound levothyroxine sodium is surprisingly favoured if the active compound is employed in micronized form. Levothyroxine sodium is customarily very sparingly soluble both in water and also in ethanol. With a particle size between 5 µm and 25 µm (to 95%), however, a release of the active compound takes place in Test 1 to > 90% (phosphate buffer) and in Test 2 to > 80% (water).

Surprisingly, the composition according to the invention can also be prepared without the use of organic solvents. If the water used in the process according to the invention is replaced by an organic solvent such as, for example, methanol, a decline in

the content of levothyroxine sodium by 10% is moreover seen in test batches after 1 year at a storage temperature of 25°C and 60% rel. humidity.

Suitable fillers for the pharmaceutical preparation according to the invention are preferably lactose, maize starch and/or microcrystalline cellulose, both as individual fillers and in combinations with one another. Particularly preferred pharmaceutical preparations, as described, contain maize starch and lactose.

The invention also relates to a process for the production of a pharmaceutical preparation comprising levothyroxine sodium and optionally liothyronine sodium, characterized in that levothyroxine sodium and optionally liothyronine sodium, which is/are present in suspended form in aqueous gelatine solution, are sprayed onto the filler(s) in a fluidized bed granulation, then a disintegrant and lubricant are admixed and the mixture is compressed to give tablets.

The invention further relates to a process as described, characterized in that the disintegrant used is croscarmellose sodium and the lubricant used is magnesium stearate.

Further excipients or auxiliaries can be added, such as, for example, binding agents, antioxidants, colorants, lubricants, sweeteners and/or aromatic substances.

Preferred glidants or lubricants are, for example, talc, starch, magnesium and calcium stearate, boric acid, paraffin, cocoa butter, macrogol, leucine or sodium benzoate; magnesium stearate is very particularly preferred.

The following examples relate to the production and the composition of the pharmaceutical preparation according to the invention:

Example 1

The following amounts are needed in order to prepare, for example, 2 million tablets:

Levothyroxine 100 µg	
Ingredient	Amount [kg]
Levothyroxine sodium*	0.210
Lactose monohydrate	131.80
Maize starch	50.00
Gelatine	10.00
Croscarmellose sodium	7.00
Magnesium stearate	1.00
Water, purified**	56.66

* A 5% excess dose of levothyroxine sodium was additionally included.

** The water is removed again by drying.

Preparation:

1. Gelatine is dissolved in about 90% of water at a temperature from 80 to 100°C.
Levothyroxine sodium is suspended in about 10% of the water at room temperature.
The suspension is then added to the gelatine solution at 50°C (± 5°C). The temperature of the suspension thus obtained (= granulation liquid) is 45 to 50°C.

2. Lactose and maize starch are placed in a fluidized bed granulator. The granulation liquid is sprayed over the powder. The temperature of the granulation liquid is kept between 40 and 50°C during the spraying

process. During the granulation, the temperature at the inlet is kept at approximately 70°C (± 5°C) and the temperature at the outlet is kept between 20 and 40°C. The spraying pressure is between 3 and 5 bar. After spraying, the granules are dried until a temperature of approximately 40°C is reached at the outlet.

The dry granules are then screened (1 mm) according to known methods (= mixture a).

Croscarmellose sodium and magnesium stearate are correspondingly screened. The components are then mixed with one another for 10 minutes together with mixture a in a drum mixer.

The press-ready mixture is then compressed to give tablets.

Example 2

Composition of a 100 mg (± 3 mg) tablet which contains 100 µg of levothyroxine sodium:

Levothyroxine sodium	0.100 mg
Lactose monohydrate	65.90 mg
Maize starch	25.00 mg
Gelatine	5.00 mg
Croscarmellose sodium	3.50 mg
Magnesium stearate	0.50 mg
	100.00 mg

Levothyroxine sodium is to be present in an around 5% excess dose.

Example 3

Composition of a 100 mg (± 3 mg) tablet which contains 100 µg of levothyroxine sodium:

Levothyroxine sodium	0.100 mg
Liothyronine sodium	0.020 mg
Lactose monohydrate	65.88 mg
Maize starch	25.00 mg
Gelatine	5.00 mg
Croscarmellose sodium	3.50 mg
Magnesium stearate	0.50 mg
	100.00 mg

Levothyroxine sodium is to be present in an around 5% excess dose.